A prospective study on myofiber contractility in myositis

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Muscle disorders
Study type	Observational invasive

Summary

ID

NL-OMON56586

Source
ToetsingOnline

Brief title
CONTRACT

Condition

- Muscle disorders
- Neuromuscular disorders

Synonym
idiopathic inflammatory myopathy, Myositis

Research involving
Human

Sponsors and support

Primary sponsor: Amsterdam UMC
Source(s) of monetary or material Support: Ministerie van OC&W,Argenx BV

Intervention

Keyword: Antibodies, Complement, Immunology, Myositis

Outcome measures

Primary outcome

Changes in contractile function (specific force) between 1st and 2nd biopsy after 10 to 15 weeks of treatment with standard of care immunosuppressive medication.

Secondary outcome

Imaging of the muscles:

MRI: quantitative assessment of edema, fat infilatration and contractile cross-sectional area, muscle fiber integrity and muscle fiber membrane stability.

Ultrasound: qualitative and quantitative analysis; including muscle fiber elasticity and muscle fiber direction.

Muscle biopsy:

Changes in histological markers between the first and second biopsy.

- Complement activation in muscle tissue.

- the degree of inflammatory infiltrates. In a few IMNM patients, we will also perform RNA sequencing on immune cells.

- the presence of regeneration, degeneration and necrosis.

Clinical:

Change of muscle strength over time - assessment according to Kendall and

isometric knee extension assessment.

Clinical improvement and response to treatment by using the Total Improvement

Score.

Mean daily prednisone dosage

Study description

Background summary

Myositis is an auto-immune disease affecting around 100.000 people in Europe. Patients suffer from severe muscle weakness and inflammation, heavily impacting daily activities and quality of life. Up to half of the patients develop pulmonary and cardiac conditions due to chronic multi-organ inflammation. The need for improved, patient-centered therapies is evident as current treatments are insufficient, cause side-effects and absence from work, and require intensive intramural care.

A better understanding of the pathophysiology underlying muscle weakness is key to identify contributors that should be targeted to prevent or revert this defect in an early stage. Myositis specific autoantibodies (MSA) and auto-immune pathways like interferon- and complement system cause direct muscle damage, but patients also show impaired muscle fiber contraction with unknown cause. Based on pilot data revealing reduced muscle fiber contractility in myositis patients with MSA, a two-step approach is proposed to determine the impact of MSA on muscle contractility:
1. Analyze human muscle fiber contractility from biopsies of patients with MSA including effects of standard of care immunosuppressant therapy.
2. Establish an ex vivo model of mouse muscle fiber contractility, a unique read-out for myositis based on muscular function. It enables screening for patients* MSA that impair muscle fiber contractility and proprietary compounds that restore this.

Study objective

In this clinical project we aim to fill in gaps in our knowledge on muscle fiber contractility, auto-immunity and myositis: 1) How responsive is human muscle fiber contractility following standard of care immunosuppressive treatment? 2) Is the severity of muscle fiber contractility impairment at baseline and changes thereof over time, related to clinical outcomes? 3) To what extent are muscle fiber contractility parameters associated with established parameters derived from serum, electrophysiology (EMG) and imaging

(ultrasound, MRI).

Related to this and within the context of a translational approach, we aim to examine the effects of constituents of myositis patients* sera (complete serum, total IgGs and purified auto-antibodies) on murine muscle fiber contractility, with the ambition to develop an ex-vivo model for studying MSA's and fiber contractility. Together, we hope to establish a firm knowledge base on the clinical correlates of muscle fiber contractility and to be able to further develop an ex-vivo model for myositis.

Specific aims:
1. To determine the course of muscle fiber contractility in adult patients with myositis with and without (known) myositis specific antibodies following standard of care treatment.
2. To correlate muscle fiber contractility with established serum, electrophysiological and imaging biomarkers
3. To collect blood samples for the investigation of the effect of human serum, IgG and autoantibodies on murine myofiber contractility in the context of a laboratory study.

Study design

prospective cohort study.

Study burden and risks

Aim 1 and 2:
Following a screening visit (week 0) at the outpatient clinic - which is combined with a regular care visit, patients are included after informed consent (IC). Patients will be assessed at baseline, treated with standard of care immunosuppressive medication and they will be assessed at a follow-up visit between 10 and 15 weeks after the baseline visit. Both study assessments, visit 1 and 2, will be combined with a visit in the context of regular outpatient care.

The burden of the study procedures is described below, per aim, because participants can be included for the complete study (aim 1,2 and 3) or for only a part of the study (aim 3).

The burden related to aims 1 and 2 consists of:
Week 0 (visit 1, baseline): Patients will complete the ALDS questionnaire and additional 25 cc blood will be collected during a routine venipuncture. Additionally, the following study procedures will be performed:
- extension of a routine MRI of the muscles (30 minutes longer)
- isometric knee extension strength assessment
- needle electromyography and an ultrasound of the muscles.

The first muscle biopsy is part standard care and is not a study procedure. A part of the tissue will be used for contractility measurements. In small proportion of the patients, an extra piece of tissue will be biopsied during the regular procedure for RNA sequencing of inflammatory cells.

Follow-up 10 to 15 weeks: patients will complete the ALDS questionnaire and additional 25 cc blood will be collected during a routine venipuncture. The following study procedures will be performed:
- extension of a routine MRI of the muscles (30 minutes longer)
- isometric knee extension strength assessment - needle electromyography
- ultrasound of the muscles and a muscle biopsy.
- muscle biopsy (open or needle biopsy)

The burden related to aim 3 consists of: - 120 cc of blood (all for experiments in murine myofibers), which will be collected during a routine venipuncture (as described above).

The risks associated with this study, are mostly related to the complication risk of the second biopsy; infection and bleeding. The risks are negligible.

As described in our protocol, inclusion for different parts of our research is possible:
1. Complete study as described above (aim 1,2,3)
2. Serum/plasma collection (aim 3)
3. Serum/plasma collection and extension of MRI (partially aim 2 and 3).

The results of this studies may a) provide valuable information on the relation between human muscle fiber contractility, auto-immunity and clinical outcomes, and b) contribute to the development of a disease model based on human MSA*s.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Adult patients (18-80 years) with IIM, according to the diagnostic criteria and the presence of the following antibodies.
o IMNM with anti-SRP antibodies
o IMNM with anti-HMGCR antibodies
o IMNM without MSA (seronegative)
o (Dermato)myositis with or without MSA
- Minimal disability defined as at least 10% loss on manual muscle testing (MMT) and abnormal scores on two other Core Set Measures (CSMs) of the international Myositis Assessment and Clinical Studies (IMACS) group.
- Newly diagnosed (aim 1+2), established diagnosis (aim 3).
- Without immunosuppressive medication (exceptions are allowed; duration of treatment and dosage in case of pre-treatment in combination with the medication-free time interval is at the discretion of treating physician).
- Signed informed consent.

Exclusion criteria

- Administration of IVIg in the 12 months before screening.
- Conditions that are likely to interfere with
o Compliance (legal incompetent and/or incapacitated patients are excluded)
o Evaluation of efficacy (e.g., due to severe pre-existing disability because of any other disease than myositis or due to language barrier)

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-06-2024
Enrollment:	96
Type:	Actual

Ethics review

Approved WMO Date:	12-02-2024
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-04-2025
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL82487.018.23